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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,586	03/01/2004	David G. Bermudes	872-A-US	9589

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Albert Wai-Kit Chan
Law Offices of Albert Wai-Kit Chan, LLC
World Plaza, Suite 604, 141-07 20th Avenue
Whitestone, NY 11357

EXAMINER	
VOGEL, NANCY S	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,586	BERMUDES ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 44-62 are pending in the case.

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection that were not necessitated by applicants' amendment and therefore, this action is final.

Claim Rejections - 35 USC § 112

Claims 44-48, 50-58, 60-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for particular tumor targeting Salmonella strains, and a method of using said strains, does not reasonably provide enablement for tumor-targeting Salmonella strain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

This rejection is maintained essentially for the reasons set forth in the previous Office action, mailed 6/16/05, with slight alterations made necessary by Applicant's submission of new claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance

presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 44 covers a Salmonella strain which expresses F'pilus and produces filamentous bacteriophage and is non-pyrogenic and tumor-targeting. Dependent claims 45-48, 50-58, and 60-62 recite that the strain is particular species of Salmonella, has certain mutations causing attenuation, including lipid mutation, pur mutation, and a combination thereof, that it delivers particular types of bacteriophage, that it delivers particular numbers of phage to tumors, that it is lac+ and kanamycin-resistant, and that it is present in a composition. Claim 61 recites the method for delivering filamentous bacteriophage to solid tumors using intravenous administration of said Salmonella. Claim 62 recites a kit comprising said Salmonella.

The nature of the invention is a composition comprising a tumor-targeting, non-pyrogenic, attenuated Salmonella bacterium containing a F' pilus and bacteriophage, and a method of delivering bacteriophage to solid tumors.

An analysis of the prior art

Regarding the use of bacteria as DNA delivery systems to mammalian cells, in order for such systems for be successful, the bacteria must first enter the cell and then escape from the vacuole to the cytosol. Movement from the vacuole to the cytosol is unpredictable because in many instances the bacteria are lysed by the host cell's defense system and any plasmids carried by the bacterial are degraded preventing expression of heterologous nucleotide sequences. At best it would appear that only a few cells, if any, may be transformed with DNA carried by a bacterial vehicle as Grillot-

Courvalin (Nature Biotechnology, 1998, 16:862-866) suggest that "direct introduction of DNA from bacteria to mammalian cells has been reported in very few instances" (page 865, discussion). Grillot-Courvalin support such observations by reporting that "factors such as entry route may have an effect" on DNA delivery. Grillot-Courvalin go on to report that a mouse dendritic cell line, which can internalize bacteria via micropinocytosis, did not express incoming DNA at 24 hours post-transfer. Grillot-Courvalin suggest that this failure could reflect rapid degradation of the invading bacteria by this cell type. It would appear that use of bacteria as DNA delivery vehicles is not very efficient in other cell lines as well as Grillot-Couvalin have reported that *E. coli* carrying a nucleotide sequence encoding the green fluorescent protein are only able to transform 0.3-1% of a transfected macrophage cell line. (see paragraph bridging pages 864-865). These observations are corroborated by Dietrich et al. (Nature Biotechnology, 1998, 16:181-185) who report that only about 0.03% of macrophages infected with a mutated form of *Listeria monocytogenes* express a green fluorescent protein reporter gene (page 183, column 2). Dietrich et al. also suggest that expression of a heterologous nucleotide sequence is not stable over time by observing a gradual loss of fluorescence over time. See page 183 at bottom of column 2. Dietrich report that the low efficiency of expression of GFP as compared to the number of macrophages infected may be due to the fact that only some of the attenuated bacteria infecting the host cells survive the antimicrobial milieu inside the phagosome and are able to escape into the host cell cytosol, whereas the others are totally digested, including the plasmid DNA, and that not all *Listeriae* being taken up reach the host cell

cytosol as an intact viable entity, but the plasmid DNA is still released into this compartment (see page 184 at top of column 2). Therefore, there is ample evidence in the prior art that the delivery of heterologous genes to eukaryotic cells via bacterial vectors is unpredictable and far from routine. Furthermore, the instant claims are drawn to tumor-targeting bacteria, which encompasses strains which preferably enter and survive in tumor cells as compared to normal cells.

Therefore, the state of the art as evidenced above suggests that use of bacteria as a vehicle for transferring heterologous nucleotide sequences to eukaryotic cells of an animal is undeveloped, inefficient, and unpredictable. The studies recited above demonstrate that only low efficiency of reporter gene expression occurs in cell line in vitro and only contemplate that bacteria could be used to transfer heterologous DNA sequences to the cells of an organism.

The relative skill of those in the art of recombinant DNA techniques and microbiology is high. The relative skill of those in the art of gene therapy and treatment of solid tumors using gene therapy is low.

The area of the invention is unpredictable. As discussed above, the method of gene therapy in general, and the use of bacteria as delivery systems to eukaryotic cells in vivo in particular, is highly complex and unpredictable and the skilled artisan at the time of the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect. Thus, the effectiveness of a potential new delivery system, such as tumor-targeted bacteria containing a bacteriophage, cannot be predicted in the absence of in vivo testing.

Furthermore, since the application does not clearly set forth methods for obtaining the property of tumor-targeting, which appears to depend on such unpredictable areas as bacterial adhesion to specific cells, ie tumor cells as opposed to normal cells, and survivability of said bacteria in tumor cells as opposed to bacterial death in normal cells, it would be quite unpredictable whether any particular Salmonella strain, with any particular genotype, would successfully target tumors as opposed to normal cells, including any normal cell target of Salmonella.

The present specification provides little direction or guidance to support the claimed invention. In particular it is noted that is it not clear what causes any tumor-targeting of the Salmonella strains in Example 6 of the specification. It is not clear if such targeting was selected in some undisclosed manner. The basis for the tumor targeting in the Salmonella used is not disclosed; thus it is unclear if one could readily generate such tumor targeting in other Salmonella strains or serotypes, unless it is an inherent property of all Salmonella.

Working Examples An example is disclosed wherein particular Salmonella expressing F'pilus are infected with a phagemid in which the gene of interest is green fluorescent protein (GFP) and are used to infect mammalian M2 cells. Expression of GFP is shown. Another example discloses injecting mice containing melanoma tumors with particular Salmonella that are expressing F' pilus and are infected with filamentous phage M13KO7. Tumor and liver homogenates and supernatants are compared for the presence of bacteria and the presence of phage.

The quantity of experimentation necessary to carry out the claimed invention is high since the skilled artisan could not rely on the prior art of the present specification to teach how to use the claimed method. In order to demonstrate how to use the method to target solid tumors using tumor-targeting Salmonella strains, one of skill in the art would have to determine if a gene of interest encoded by a bacteriophage and delivered by a bacteria is delivered efficiently and preferentially to the targeted tumor type. One must determine if the bacterial composition would survive and bacteria would reach the targeted tumors efficiently and specifically, and in sufficient number to achieve a therapeutic effect, rather than being targeted by the immune system to some degree, despite their attenuated pathogenicity. One would have to determine how to make Salmonella strains which specifically target tumor cells, and which do not infect or attach to normal cells. Since neither the prior art nor the specification provides the answers to all of these questions it would require a large quantity of trial and error experimentation by the skilled artisan to answer these questions.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to make the claimed strains and kits, and use the claimed method comprising administering tumor targeting Salmonella strains other than those shown in the specification to specifically deliver filamentous phage to tumor cells, in Example 6.

Claims 49, 50 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The application discloses strains and bacteriophage that are encompassed by the definitions for **biological material** set forth in 37 C.F.R. 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. 1.801 through 1.809.

It is unclear whether this biological material is known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F. R. 1.801-1.809, in the form of a declaration of applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the

effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Claims 44-48, 50-58, and 60-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description published in the Federal Register (Volume 66, Number 4, Pages 1099-1111). Claim 44 is drawn to an attenuated, non-pyrogenic, tumor targeting Salmonella strain having the F'pilus and which produces filamentous bacteriophage.

The specification has disclosed multiple properties encompassed by the tumor-targeting definition at page 5 of the specification which includes serum resistance,

facultative anaerobiasis, susceptibility to the hosts defensive capabilities to limit replication I normal tissues but not within tumors where the host defensive capabilities may be impaired, attenuation of virulence whereby susceptibility to the host defenses may be increased and the bacteria is tolerated by the host but does not limit intratumoral replication, invasive capacity towards tumor cells, motility to aid in permeation throughout the tumor, antibiotic sensitivity, and low reversion rats of phenotypes. Claims 44- 48, 50-58, and 60-62 are genus claims in terms of Salmonella strains which are tumor targeting, attenuated and non-pyrogenic, and kits encompassing said Salmonella, and a method of delivering filamentous phage to a tumor using said Salmonella strains. The disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the tumor-targeting, non-pyrogenic, and attenuated Salmonella based on the teachings of the specification. While the specification provides an example of a strain in Example 6 which appears to deliver filamentous phage to tumor cells in greater amounts than to normal cells, there is no disclosure of which modifications of Salmonella could be made which result in such tumor targeting. Therefore, the specification does not describe the genus of tumor-targeting, attenuated, non-pyrogenic Salmonella in such full, clear, concise and exact terms so as to indicate that Application had possession of the claimed bacteria and method at the time of filing the present application. Thus, the written description requirement has not been satisfied.

Vas-Cath V. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed structure of the encompassed genus of tumor targeting Salmonella , and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Col. Ltd.,* 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the particular tumor targeting Salmonella of Example 6, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim 49 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification as originally filed does not provide support for the invention as now claimed: "the group consisting of YS72 (ATCC Accession No. 55680)". This a new matter rejection. The specification does not provide sufficient blazemarks nor direction for the instant product encompassing the above-mentioned limitations, as currently recited. The instant claim now recites limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112. It is noted that at page 42, lines 24 and 34, there is no disclosure of a strain "YS72".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 49, and by dependence, claim 59, are vague and indefinite in the recitation of "the Salmonella typhimurium is derived from..." since the number and types of steps involved in said deriving are not known, and therefore it cannot be determined what the intended metes and bounds of the claimed subject matter are.

Response to Arguments

Applicant's arguments filed 9/16/05 have been fully considered but they are not persuasive.

Applicants have argued that the instant invention is directed toward deliver of phage rather than delivery of DNA, and that therefore the arguments set forth in the previous Office action are not valid (page 9 of the response). However, it is maintained that the same unpredictability and areas of recognized difficulties exist for bacteria delivering phage, as for bacteria delivering DNA. While the claims may have been amended to remove the language "gene of interest", these difficulties and unpredictable factors remain. Applicants further point out references in which "phage were attempted to be delivered to tumors, and how they failed to do provide a methodology for the delivery of filamentous phage directly to tumors in high numbers by intravenous administration" (page 9). This does not lend support to applicant's argument that the state of the prior art supports enablement. Applicant's statement that "tumor-targeting strains of Salmonella are available from the ...ATCC." (page 10) is not supported by evidence, and it remains undisclosed what the characteristics of such strains would be. Regarding predictability, applicants point to their previous arguments, and repeat that

the Examiner's arguments are based on DNA delivery, not delivery of phage (page 11). As was stated previously, the same unpredictability and difficulties remain with phage delivery, as opposed to DNA delivery. Both methods involve the same process of delivering bacteria which "target" tumors, in vivo, and enter the cell and survive to "deliver" either DNA or phage. For the reasons set forth above in the rejection, it is maintained that the scope of the claims has not been enabled by the specification.

Regarding the rejection under 35 USC 112, first paragraph, written description, applicants have argued (page 17) that their arguments are similar to those set forth in the response to the rejection of claims under 35 USC 112 first paragraph, enablement. For the reasons set forth above, the arguments are not found convincing and the rejection is maintained.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JAMES KETTER
PRIMARY EXAMINER

JAMES KETTER
PRIMARY EXAMINER